UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/928,198	08/10/2001	James Arthur Hoffmann	X12383N	6700

25885 7590 01/10/2006

ELI LILLY & COMPANY
PATENT DIVISION
P.O. BOX 6288
INDIANAPOLIS, IN 46206-6288

EXAMINER	
DEBERRY, REGINA M	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 01/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/928,198	HOFFMANN ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *132-174* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *132-174* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Status of Application, Amendments and/or Claims

The amendment filed 26 August 2005 has been entered in full. Claims 1-131 are cancelled. New claims 132-174 have been added. Claims 132-174 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

The rejection to claim 128 under 35 U.S.C. 103(a) as being unpatentable over Keene *et al.*, The Journal of Biological Chemistry Vol. 264/9:4769-4775 in view of Skrabanja *et al.*, EP 0853 945 A1 and Andya *et al.*, US Patent No. 6,267,958 B1, as set forth at page 3 of the previous Office Action 27 May 2005 is *withdrawn* in view of the amendment (26 August 2005).

The provisional rejection to claim 128 under the judicially created doctrine of double patenting over claims 159 and 160 of copending Application No. 09/744,431 in view of Keene *et al.*, The Journal of Biological Chemistry Vol. 264/9: 4769-4775 (1989), Skrabanja *et al.*, EP 0853 945 A1 and Andya *et al.*, US Patent No. 6,267,958 B1, as set forth at page 3 of the previous Office Action 27 May 2005 is *withdrawn* in view of the amendment (26 August 2005).

The rejection to claims 129-131 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement (new matter), as set forth at page 3 of the previous Office Action 27 May 2005 is *withdrawn* in view of the amendment (26 August 2005).

NEW CLAIM REJECTIONS:

Claim Rejections - 35 USC § 112, First Paragraph, Written Description, New Matter

New claims 132-151, 158, 160-167, 171-174 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The previous claims were directed solely to pharmaceutical compositions comprising FSH. Applicant's amendment, filed 26 August 2005, adds 43 new claims (including methods of treating/administering, methods of making) and fails to provide any direction for the written description for the mentioned "limitations". The Examiner cannot locate the exact wording or connotation of all of the instant claims. The specification as originally filed does not provide support for the invention as now claimed:

(claim 132) "first administering to the patient from said vial a first quantity of formulation, the first quantity of formulation, the first quantity including a pharmaceutically-effective amount of FSH; and second administering to the patient from said vial a second quantity of formulation, the second quantity including a pharmaceutically-effective amount of FSH; the second quantity being administered to said patient greater than 24 hours after said first administering".

(claim 139) "injecting a first portion of the pharmaceutical composition into a human in need of ovarian follicle or testicular stimulation, said injecting a first portion providing an effective dose of biologically active human FSH for ovarian follicle or testicular stimulation in humans, injecting a second portion of the pharmaceutical composition into the human at least 24 hours after said injecting a first portion, said injecting a second portion providing an effective dose of biologically active human FSH for ovarian follicle or testicular stimulation in the human".

(claim 143) "holding the pharmaceutical composition for at least 24 hours; and after said holding, administering an amount of said pharmaceutical composition to a human so as to provide an effective dose of human FSH for ovarian follicle or testicular stimulation in the human"

(claim 147) "first administering a first portion of the pharmaceutical composition to a patient in need of ovarian follicle or testicular stimulation, said administering providing an effective dose of biologically active human FSH for ovarian follicle or testicular stimulation in the patient, second administering a second portion of the pharmaceutical composition to the patient at least 24 hours after said first administering, said second administering providing an effective dose of biologically active human FSH for ovarian follicle or testicular stimulation in the patient"

(claims 139, 143, 147, 160, 167, 174) "ovarian follicle or testicular stimulation in humans"

(claims 141, 145, 150, 162, 165, 173) "wherein greater than 99% of the FSH protein particles in the pharmaceutical composition have an average diameter of about

5.7 nanometers even after incubation of the pharmaceutical composition at 37°C for 24 hours"

(claim 158) "providing a lyophilized mixture of FSH and a lyoprotectant"

(claims 140-142, 144-146, 149-151, 161-166, 171-173) "a composition comprising benzyl alcohol and human FSH (concentrations 5.0ug/ml to 2mg/ml), wherein the FSH consists of an α-subunit having SEQ ID NO:5 and a β-subunit having SEQ ID NO:6, wherein greater than 99% of the FSH protein particles in the pharmaceutical composition have an average diameter of about 5.7 nanometers even after incubation of the pharmaceutical composition at 37°C for 24 hours" or "wherein greater than 99% of the FSH protein particles in the pharmaceutical composition are provided by said biologically active heterodimeric form"

The specification as filed does not provide a written description or set forth the metes and bounds of this "limitations". The specification does not provide direction for the instant methods encompassing the above-mentioned "limitations" as they are currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as-filed.

Applicant is required to cancel the new matter in the response to this Office action. Alternatively, Applicant is invited to provide *specific* written support for the "limitations" indicated above or rely upon the limitations set forth in the specification as filed.

Claim Rejections - 35 USC § 103

New claims 152-160, 167-170 and 174 are rejected under 35 U.S.C. 103(a) as being unpatentable over Keene *et al.*, The Journal of Biological Chemistry Vol. 264/9: 4769-4775 (1989) (reference of record) in view of Andya *et al.*, US Patent No. 6,267,958 B1 (reference of record) and Skrabanja *et al.*, EP 0853 945 A1 (reference of record).

The instant claims are drawn to 1) a method comprising preparing an aqueous pharmaceutical formulation comprising human FSH and benzyl alcohol, said human FSH consisting of an α-subunit having SEQ ID NO:5 and a β-subunit having SEQ ID NO:6 held together by noncovalent interactions, said human FSH being present as the biologically-active, heterodimeric protein form of human FSH at a concentration of 5.0ug/ml to 2 mg/ml, said benzyl alcohol being present in an amount effective to act as a preservative for the formulation; and placing the formulation into a vial and 2) a pharmaceutical composition comprising an aqueous diluent, benzyl alcohol and human FSH (concentrations 5.0ug/ml to 2mg/ml), wherein the FSH consists of an α-subunit having SEQ ID NO:5 and a β-subunit having SEQ ID NO:6, held together by noncovalent interactions.

Keene *et al.* teach the expression of biologically active recombinant human FSH (abstract, page 4769, 3rd paragraph; page 4771, 3rd paragraph and 6th paragraph). Human FSH α-subunit is SEQ ID NO:5 (1-92 amino acids). Human FSH β-subunit is SEQ ID NO:6 (1-111 amino acids). Keene *et al.* describe the construction and expression of human FSH α and β-subunits (page 4770, first paragraph). Recombinant

FSH protein inherently meets the limitation "held together by noncovalent interactions". Keene *et al.* teach biological activity of recombinant human FSH (page 4772, 2nd paragraph-page 4773 and Figures 6, 7). Keene *et al.* do not disclose a formulation comprising FSH and benzyl alcohol, multi-dose administration, storage time periods, FSH concentrations or vials.

Andya *et al.* teach stable lyophilized protein formulations, which when reconstituted generate a stable multi-use formulation (column 1, lines 52-column 2, line 9). The reconstituted formulation may be used as a multi-use formulation (column 2, lines 20-30). Andya *et al.* teach FSH as a suitable protein in the formulation (column 6, lines 44-50). Andya et al. teach that the protein which is formulated is pure (column 7, lines 18-25). Andya et al. teach storage time periods which overlap the instant claims (column 8, line 45-column 9, line 7). Andya *et al.* teach that a preservative can be added to the diluent to reduce bacterial action in the reconstituted formulation, thus facilitating the production of a multi-use reconstituted formulation. Andya et al. teach that the most preferred preservative is benzyl alcohol (column 9, lines 46-58). Andya et al. teach an article of manufacture comprising a vial or a pen-injector device. Andya et al. teach time courses of administration that overlap with the instant claims (column 17, lines 48-67 and column 18, lines 24-50). Andya et al. do not teach concentrations of FSH.

Skrabanja *et al.* teach pharmaceutical compositions comprising FSH in an aqueous solution for follicular maturation (abstract; page 2; page 3, lines 15-18, 35-38 and page 4, lines 11-13). Liquid FSH comprises includes human recombinant FSH

(page 3, lines 35-54). Skrabanja *et al.* teach concentrations of FSH which overlap the concentrations in the instant claims (page 5, lines 5-14). Skrabanja *et al.* also teach an article of manufacture comprising a vial or a pen-injector device. The formulation can be in the form of a cartridge for multiple uses (page 5, lines 21-45).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Keene, Skrabanja and Andya to make the instant invention of a pharmaceutical acceptable solution formulation suitable for multi-use comprising human FSH and benzyl alcohol. The motivation and expected success is provided by Keene, Skrabanja and Andya. The expression of biologically active recombinant human FSH (Keene *et al.*) avoids the need of purifying FSH from natural sources. Andya *et al.* teach that formulations comprising FSH, which have preservatives such as benzyl alcohol, reduce bacterial action. The cartridge of Skrabanja *et al.* provides the convenience of stable multiple uses of FSH pharmaceutical formulations.

Applicant argues that newly submitted claims are distinguishable over the prior art and discusses the history of FSH. Applicant states, "as suggested by the Examiner, the claims incorporate limitations related to the stability of the formulations, and are distinguishable form the prior art on that basis". Applicant's arguments have been fully considered but are not deemed persuasive for the reasons discussed above in the 35 USC 103 rejection and reasons of record. Lastly, the Examiner is unclear *exactly when* a suggestion was made to Applicant to incorporate limitations related to the stability of the formulations.

The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RMD
1/4/06

Marianne P. Allen
MARIANNE P. ALLEN
PRIMARY EXAMINER
1/9/06
AU1647